POSTER

Antiplatelet Agents

(Abstract Nos 108-115)

TCT-108

Clopidogrel Hypersensitivity Reactions: Histologic Characterization and Management With Short Term Steroids

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Background: Patients with hypersensitivity reactions to Clopidogrel (CS) present difficulty in management. Although, successful desensitization has been reported, the type and nature of CS is poorly understood. In this report, we characterize CS after stenting and describe management of these patients using oral steroids without Clopidogrel discontinuation or desensitization.
Methods: All patients with CS after coronary stenting at a tertiary care hospital were referred to a designated Clopidogrel allergy clinic for management. All patients referred to the clinic since February 2007received a two week tapering course of oral prednisone after initial evaluation and underwent close clinical and laboratory follow up with assessment. White blood cell and eosinophil counts were determined at time of CS and in steady state after prescribed duration of dual antiplatelet therapy was completed. Punch biopsy of affected area was performed in 12 patients at initial presentation and patch testing with various Clopidogrel concentrations was performed in 16 patients after a minimum drug free period of 4 weeks.
Results: 72 patients with CS were treated at the clinic from February 2007 to April 2010. 92% of patients presented with a pruritic, erythematous cutaneous eruption affecting torso and proximal extremities starting at 5±1 day after Clopidogrel initiation. The lymphocyte and eosinophil count at the time of CS were not different from baseline and steady state. Skin biopsy of CS showed epidermal spongiosis, perivascular and interstitial infiltrates consisting of lymphocytes, histiocytes and neutrophils. All patients were treated with a two week tapering course of prednisone starting at 30 mg twice a day for five days. Complete resolution of CS was observed in all patients with no recurrence after stopping steroids. Re-exposure to Clopidogrel after discontinuation produced a recurrence of previous reaction in four patients. The patch testing was positive at 48 hours in 12 patients with histology consistent with delayed hypersensitivity and similar to that seen at initial presentation.
Conclusion: CS is characterized by a pruritic erythematous rash on day 4-6 in most patients. The adverse reaction is reproducible with patch testing and histology consistent with a delayed hypersensitivity type reaction. In addition, all patients with CS can be successfully treated with short term course of oral steroids without Clopidogrel discontinuation.

TCT-109

Development of an Antithrombotic-Eluting RES TECHNOLOGYTM Stent

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Background: Instead of a conformal coating, the NEVO™ Sirolimus-eluting Coronary Stent utilizes hundreds of reservoirs filled with sirolimus admixed in a bioabsorbable poly (lactic-co-glycolic) acid (PLGA) polymer matrix that is programmed to degrade safely in as little as 90 days. The RES TECHNOLOGY™ platform allows for concurrent delivery of multiple drugs with independent release kinetics and provides for directional control of drug release. A single drug eluting stent that combines sirolimus and an anti-platelet agent could provide additional therapeutic benefit to high-risk patients.
Methods: We developed a dual-drug eluting stent that releases sirolimus abluminally and a potent antiplatelet agent luminally from alternating reservoirs positioned on the stent struts. The antiplatelet agents examined were cilostazol (a phosphodiesterase (PDE) III inhibitor) and tirofiban (a glycoprotein IIb/IIIa inhibitor). Formulations were developed to provide controlled elution of the antiplatelet agent and release kinetic profiles were determined. The *in vitro* antithrombotic performance was investigated using two blood flow loop models.
Results: The antiplatelet agents were formulated in a PLGA matrix to attain controlled release luminally from the stent. Total cilostazol release duration could be controlled from 1 to 6 weeks, while for tirofiban the release duration was from 3 days to 3 weeks. Both antiplatelet agents showed a reduction in stent thrombosis of 40% to 60% vs. a polymer-only filled control as measured by radio-labeled platelet counts in bovine blood loop studies.
Conclusions: Prototype drug-eluting stents utilizing RES TECHNOLOGY™ were successfully developed and shown to concurrently deliver two therapeutic agents independently with directional control of drug release. Blood loop studies have demonstrated the *in vitro* antithrombotic efficacy of these stents compared to polymer-only filled control stents. Both cilostazol and tirofiban were effective antithrombotic agents when compared to polymer-only filled stents. A dual sirolimus/anti-platelet eluting stent based on RES TECHNOLOGY™ could offer additional clinical benefit to patients at higher risk of developing stent thrombosis.

TCT-110

Clinical Outcomes of Warfarin Plus Dual Antithrombotic Therapy Versus Dual Antithrombotic Therapy Alone Following Percutaneous Coronary Intervention

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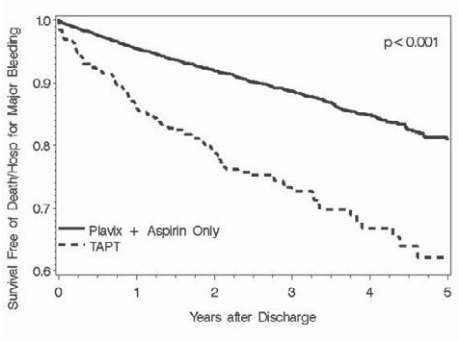
Background: Warfarin plus dual antithrombotic therapy (W-DAT) is occasionally prescribed after PCI. Limited data exist as to the long term safety and efficacy outcomes of W-DAT versus DAT in patients undergoing PCI. We sought to compare the clinical outcomes of patients treated with W-DAT (warfarin, aspirin and clopidogrel) versus DAT (aspirin and clopidogrel) in the contemporary PCI era.
Methods: Retrospective cross-sectional analysis of prospective data from 4936 patients who underwent PCI at Mayo Clinic Rochester from April 2003 through March 2008. The primary outcome was the composite of all cause mortality plus hospitalization for major bleeding. Major bleeding was defined using the ACUITY definition. The secondary outcomes were all cause mortality and a composite of all cause mortality plus hospitalization for any bleeding. Median follow up was 35 months (interquartile range: 17-48 months).
Results: Of the 4936 patients, 391 received W-DAT and 4545 received DAT. At 5 years, there were 626 composite events for the primary outcome. At baseline, the W-DAT cohort had a significantly higher clinical and angiographic risk profile. In multivariate Cox proportional hazards regression analysis, W-DAT was associated with higher all cause mortality or hospitalization for major bleeding, when compared to DAT (HR = 1.64, 95% CI = 1.31-2.06, p < 0.001). Both secondary outcomes favored DAT (p < 0.001).



Conclusion: This is the largest study comparing the long term bleeding and mortality outcomes of W-DAT to DAT, in a contemporary PCI population. In this analysis, W-DAT was significantly associated with death or hospitalization for any bleeding. Importantly, the risk of adverse events with W-DAT continued to increase up to 5 years of follow-up. This association has important clinical implications and will benefit from further prospective evaluation. Page 1

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Direct Vasoactive Properties Of Thienopyridine Derived Nitrosothiols

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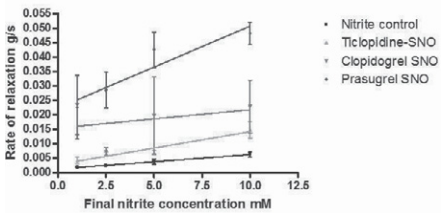
Objective: Ticlopidine, Clopidogrel and Prasugrel exhibit a critical thiol group in the active form that binds to the $P2Y_{12}$ receptor to inhibit platelet activation. They form an acidic aqueous solution and have free thiol - ideal conditions for nitrosothiol (SNO) formation ***directly*** from the base drug in the presence of a suitable NO^+/NO supply, without ***enzymatic*** biotransformation. We investigated the potential vasoactive properties of thienopyridine derived nitrosothiols in an isolated vascular preparation.
Methods: Ticlopidine (Ticlopidin), clopidogrel ($Plavix_{tm}$) and prasugrel ($Efient_{tm}$) were crushed into aqueous solution and sodium nitrite added to form thienopyridine-SNO. Ozone-based chemiluminescence techniques were utilised to detect NO release from the SNO produced. An isolated aortic vessel preparation was used to test vasoactivity of Thienopyridine-SNO.
Results: Both Prasugrel-SNO and Clopidogrel-SNO induced significant and immediate relaxation, with prasugrel-SNO induced relaxation more evident at lower concentrations of nitrite substrate (2.5mM ($p<0.001$ vs control) versus 10mM clopidogrel-SNO ($p<0.05$ vs control)). The extent of Prasugrel-SNO relaxation (Rmax) was also greater ($p < 0.001$). Ticlopidine formed very little SNO and did not show any significant relaxation when added to pre constricted rings at all concentrations tested (1, 2.5, 5 and 10 mM - $p > 0.05$) Prasugrel-SNO exhibited more potent vasoactivity by enhanced prasugrel-SNO formation



Conclusion: Clopidogrel-SNO and Prasugrel-SNO have nitrovasodilator properties by donating NO^+/NO to relax vascular smooth muscle via the soluble guanylate cyclase pathway. This may be important to our understanding of the direct pharmacological effectiveness of thienopyridines on vascular and platelet function and explain the postulated pleiotropic effects.

TCT-112

Dual Antiplatelet Therapy Cessation due to Bleeding Complication is Related to Long-Term Clinical Outcome Following Percutaneous Coronary Intervention

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Background: Dual antiplatelet of aspirin plus thienopyridine is a standard therapy following percutaneous coronary intervention (PCI). However, thienopyridine is sometimes compelled to be stopped due to side effects or other reasons. We studied the relation between reasons for thienopyridine cessation and the long-term outcome.